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Comparative assessment of vitamin D and parathyroid hormone as risk factors of myocardial infarction and their correlation with lipid profile

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ABSTRACT

Background: Vitamin D (VitD) inadequacy has recently been implicated in the development of myocardial infarction (MI). Parathyroid hormone (PTH), which works closely with VitD in regulating calcium balance, has also been shown to exert cardiovascular effects. Clinical data on serum VitD and PTH in MI and their association with lipid profile are wanting, particularly in the local context. The present study assessed serum vitamin D and PTH in MI and determined their correlation with lipid profile parameters. *Materials and Methods:* The cross-sectional comparative study assessed serum vitamin D, PTH and lipid profile in patients (n=30) with recent MI (< 1-month history). Comparisons were made with healthy age-matched controls (n=30) using independent sample t-test while correlations were determined using Pearson's correlation. *Results:* MI patients had lower VitD (27.52 $\pm$ 12.99 ng/mL vs. 51.10 $\pm$ 6.48 ng/mL; p=0.001) and higher PTH levels (45.51 $\pm$ 25.72 pg/mL vs. 19.90 $\pm$ 8.50 pg/mL; p-0.001). Low VitD and high PTH correlated with deranged lipid profile overall. *Conclusion:* Low VitD and high PTH potentially increase the risk of MI through disturbance of lipid balance. Future studies employing supplementation with VitD and control of PTH may help find their role in mitigating the risk of MI.

Keywords: Myocardial infarction, Vitamin D, Parathyroid hormone, Dyslipidemia, Cardiovascular diseases

1. INTRODUCTION

Atherosclerotic cardiovascular diseases (CVDs) are a serious global health concern. Myocardial infarction (MI), a common and critical manifestation of atherosclerotic CVDs, remains a leading cause of mortality and morbidity worldwide (Virani et al., 2020). Obesity, smoking, hypertension, unhealthy dietary habits, deranged lipid profile, sedentary lifestyle and psychosocial problems are some of the well-known risk factors of MI (Bhardwaj et al., 2014; Shah et al., 2020a). Vitamin D (VitD) and parathyroid hormone (PTH) are involved in skeletal mineral homeostasis of calcium and bone metabolism, through their reciprocal regulation. Dermal production of cholecalciferol is a chemical form of Vit D, after sunlight exposure the predominant source of vitamin D in humans. Cholecalciferol synthesized by skin cells undergoes double hydroxylation to yield calcitriol, the activate form of VitD (Buyuker, 2019). Besides its effects on bone metabolism, VitD has recently been implicated in a wide range of physiological functions on various body systems including immune, nervous, cardiovascular and metabolism with potential impact on conditions including cancer, infection, neurodegeneration, insulin resistance and CVD (Zmijewski, 2019). Advanced age, less sunlight, dietary insufficiency, smoking and/or other co-morbidities have been highlighted as risk factors for VitD deficiency (Parva et al., 2018).

VitD has been shown to exert direct and indirect effects on cardiovascular health. VitD receptors are present in heart and are involved in the regulation of cardiomyocyte proliferation. VitD also suppresses renin-angiotensin-aldosterone system (Adhikari and Ghimire, 2018). Additionally, low serum vitamin D has also been suggested as a potential cardiometabolic marker due to its association with cardiovascular risk factors such as hypertension, dyslipidemia, insulin resistance and obesity (Fanari et al., 2015; Shah et al., 2020b). Low serum levels of VitD have been shown to put individuals at a higher risk of MI after controlling for the established risk factors but loco-regional data are ambiguous (Akhtar et al., 2019; Shereef and Kandeel, 2019). While most of these studies have investigated the association of cardiovascular health with VitD status, similar work on parathyroid hormones (PTH) is lacking particularly in the loco-regional context. Closely associated with VitD, PTH, secreted by the parathyroid glands, regulates renal calcium reabsorption and facilitates activation of VitD in the kidneys (Goltzman, 2018). PTH has also been shown to exert effects on the cardiovascular system. PTH induces apoptotic transformation and mediates hypertrophic changes in cardiomyocytes through PTH receptors located in the myocardium (Fujii, 2018). Elevated PTH levels have been linked, albeit inconsistently, to adverse outcomes in patients with acute coronary syndromes (ACS) including MI (Fujii, 2018; Hoque et al., 2020). The present work explored serum VitD, PTH and lipid profile in patients with MI and compared them with healthy individuals from the local population without CVDs.

2. MATERIALS AND METHODS

This cross-sectional analytical study was conducted at University of Hafr Al Batin, Saudi Arabia between the duration May 2020 to November 2020 according to the World Medical Association Declaration of Helsinki. Subjects (n=60) were enrolled in the study via non-random convenience sampling and written informed consent was obtained from the study participants prior to recruitment. Adult patients (n=30) between the ages of 18-75 years with a recent MI (<1-month history) and without any previous history of CVDs, recruited from Rehmat ul lil Alameen Institute of Cardiology, Lahore, Pakistan formed the group 1. Age and sex matched healthy control participants (n=30) without any history of CVDs recruited from the local population of Lahore, Pakistan formed the group 2. Subjects suffering from clinical disorders associated with reduced Vit D levels including osteomalacia, malabsorption states, liver diseases, renal dysfunction and parathyroid disorders were excluded.

5 ml venous fasting blood sample was collected from each participant for the quantification of serum Vit D, parathyroid hormone (PTH) and lipid profile parameters including serum total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) using commercially available assay kits for each. Serum levels of calcium and phosphate were also determined. Sun exposure was estimated using a validated sun exposure questionnaire (Patwardhan et al., 2018). The questionnaire accounted for time and duration of sunlight exposure, nature of work, wearing full-sleeve/half-sleeve shirts and covering of face by a helmet/cap/veil or scarf. Sun exposure was calculated for a typical working day and individuals were categorized as having sunlight exposure <1 h/day, sunlight exposure 1-2 h/day, and sunlight exposure >2 h/day. Body mass index (BMI) (Nuttall, 2015), weight in kilograms divided by height in meters squared) was also calculated for each participant to categorize them as normal weight (BMI18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2), and obese (BMI ≥30 kg/m^2). All data were recorded in a confidential and anonymous manner.

The collected data were entered twice and compared for errors before analysis using SPSS version 23. Normality was assessed using Shapiro-Wilk test. Mean± Standard deviations (SD) of quantitative variables were calculated for both groups and independent sample T-test was applied to observe group mean differences. Pearson's correlation was used to ascertain correlation between quantitative variables. Qualitative variables were described as frequencies and percentages. A p-value of < 0.05 was considered as statistically significant.

3. RESULTS

24 (40%) of the study participants were females and 36 (60%) were males with equal distribution within groups (Table 1). Mean age of the study population was 45.02 ± 12.889 years (range 18-75 years) with no difference in the mean age between groups (Group 1, 47.30 + 9.502 years vs. Group 2, 42.73 + 15.391 years; p=0.172, Table 2). Based on their BMI values, 30 (50%) of the study participants were normal weight, 26 (43.33%) were overweight and 4 (6.66%) were obese (Table 1). No difference was observed in the mean BMI values between groups (Group 1, 26.19± 2.91 kg/m^2 vs. Group 2, 24.91 ± 2.24 kg/m^2; p= 0.062, Table 2). Out of the 60 study participants,35 (58.33%), 17 (28.33%) and 8 (13.33%) had average daily sun exposure less than 1 hour, between 1-2 hours and more than 2 hours respectively. Fewer group 1 subjects had higher average daily sun exposure as compared to group 2 (Table 1).

Table 1 Distribution of participants based on gender, BMI and average daily sun exposure

Parameter	Category	Group 1 (MI) n (Percentage)	Group 2 (Control) n (Percentage)
Gender	Female	12 (20%)	12 (20%)
	Male	18 (30%)	18 (30%)
Body Mass Index (BMI)	18.5-24.9 kg/m^2	12	18
	25-29.9 kg/m^2	14	12
	≥30 kg/m2	4	0
Average Sun Exposure	<1 h/day	21 (70%)	14 (46.67%)
	1–2 h/day	7 (23.33%)	10 (33.33%)
	>2 h/day	2 (6.67%)	6 (20%)

Mean serum VitD levels were significantly lower (27.52 + 12.99 ng/mL vs. 51.10 + 6.48 ng/mL; p=0.001) while mean serum PTH levels were significantly higher (45.51 + 25.72 pg/mL vs. 19.90 + 8.50 pg/mL; p-0.001) in group 1as compared to group 2 (Table 2, Figure 1). Serum phosphate was lower in group 1 (3.92 + 1.19 mg/dL vs. 4.78 + 0.76 mg/d; p=0.002) but no difference in serum calcium was observed between groups (Table 2, Figure 1). Higher serum TC, LDL-C and TG and lower serum HDL-C were observed in group 1 in comparison with group 2 (Table 2, Figure 2).

Table 2 Group comparisons of age, BMI and serum biochemical parameters

Parameter	Mean ± SD		p-value
	Group 1	Group 2	
Age (in years)	47.30 ± 9.502	42.73 ± 15.391	0.172
BMI (kg/m^2)	26.19 ± 2.91	24.91 ± 2.24	0.062
VitD (ng/mL)	27.52 ± 12.99	51.10 ± 6.48	0.001*
PTH (pg/mL)	45.51 ± 25.72	19.90 ± 8.50	0.001*
Calcium(mg/dL)	9.46 ± 0.42	9.68 ± 0.78	0.190
Phosphate(mg/dL)	3.92 ± 1.19	4.78 ± 0.76	0.002*
TC (mg/dL)	190.93 ± 41.10	128.56 ± 14.00	0.001*
LDL-C (mg/dL)	115.16 ± 28.46	79.06 ± 15.21	0.001*
HDL-C (mg/dL)	35.76 ± 5.28	46.00 ± 4.79	0.001*
TG (mg/dL)	178.33 ± 55.95	110.40 ± 13.79	0.001*

*Difference is significant at p<0.05

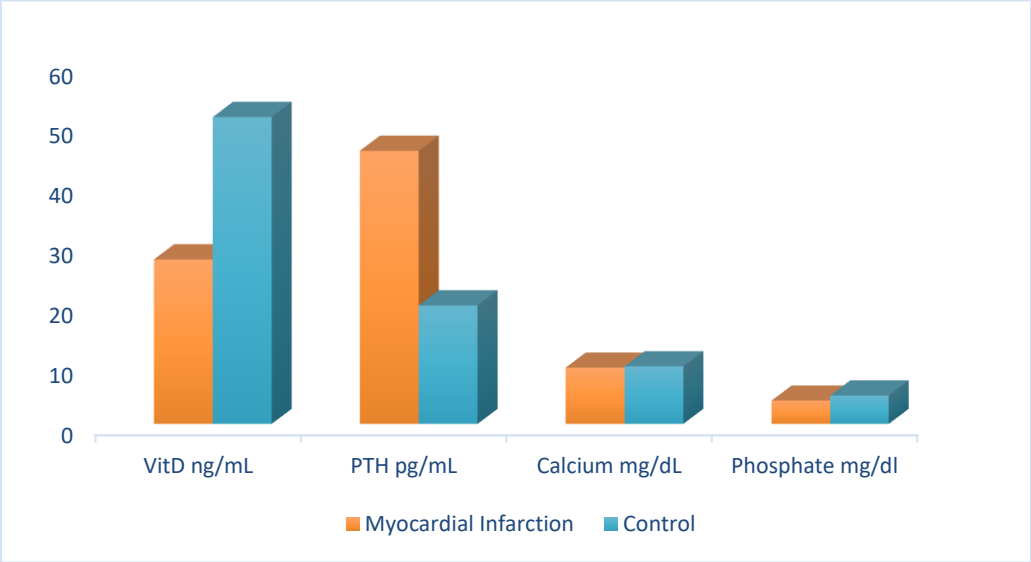

Figure 1 Mean serum vitamin D, parathyroid hormone, calcium and phosphate levels in patients with myocardial infarction and healthy controls

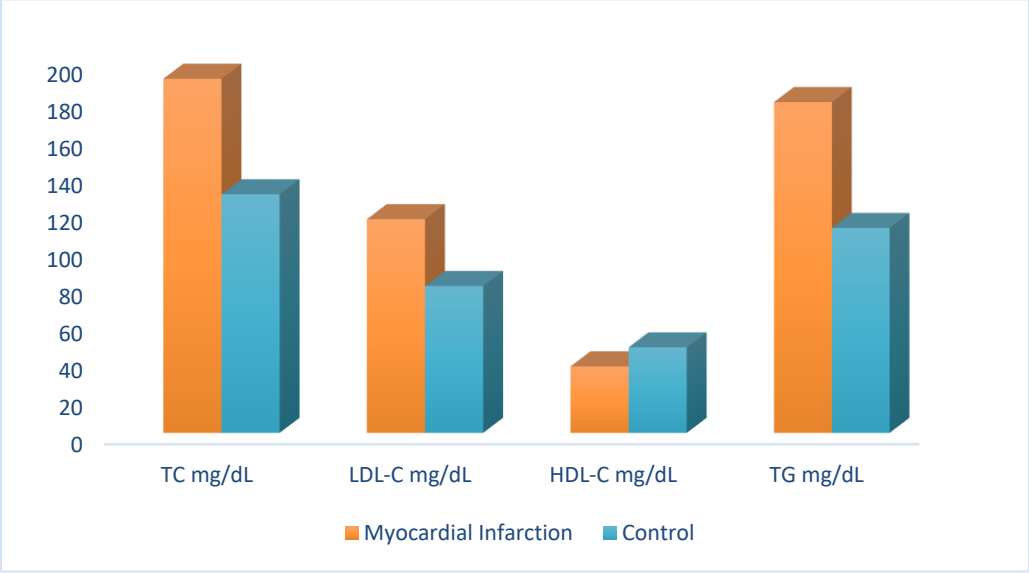

Figure 2 Mean serum levels of lipid profile parameters in patients with myocardial infarction and healthy controls

Overall, serum Vit D was negatively correlated with serum TC, LDL-C, TG and PTH and positively correlated with serum phosphate (Table 3). Serum PTH was positively correlated with TC, LDL-C and TAG and negatively correlated with serum VitD and HDL-C (Table 3).

Table 3 Correlations of serum vitamin D and PTH with biochemical parameters

Biochemical Parameters		Overall		Group 1 (MI)		Group 2 (Control)	
Parameter 1	Parameter 2	R	p-value	R	P	R	P
VitD	TC	-0.519	0.000*	0.001	0.996	0.400	0.028
	LDL-C	-0.408	0.001*	0.145	0.444	0.092	0.629
	HDL-C	0.541	0.000*	-0.062	0.743	0.110	0.563
	TG	-0.417	0.001*	0.159	0.400	0.097	0.608
	PTH	-0.495	0.000*	-0.196	0.300	0.279	0.135
	Calcium	0.241	0.063	-0.036	0.851	0.479	0.007
	Phosphate	0.415	0.000*	0.197	0.297	0.165	0.383

PTH	TC	0.380	0.003*	-0.033	0.863	-0.127	0.503
	LDL-C	0.513	0.000*	0.285	0.126	0.072	0.705
	HDL-C	-0.322	0.012*	0.157	0.406	0.144	0.447
	TG	0.440	0.000*	0.151	0.427	-0.227	0.228
	VitD	-0.495	0.000*	-0.196	0.300	0.279	0.135
	Calcium	-0.223	0.087	-0.071	0.709	-0.445	0.014*
	Phosphate	-0.293	0.023*	-0.076	0.691	-0.175	0.356

* Difference is significant at $p<0.05$

4. DISCUSSION

MI is a leading presentation of CVDs with profound global health-economic burden (Virani et al., 2020). The present study investigated serum VitD, PTH and lipid profile parameters in patients with MI and made comparisons with healthy individuals without history of MI. Lower serum VitD levels and higher serum PTH levels were seen in MI patients as compared to the healthy control subjects. Expectedly and as reported previously, our findings revealed an inverse correlation between VitD and PTH overall (Al-Daghri et al., 2020). Furthermore, our results showed low serum concentration of VitD and high serum concentration of PTH to be correlated with dyslipidemia. Inadequacy of Vit D has previously been linked with various forms of CVD (Kheiri et al., 2018; Rai and Agrawal, 2017). Consistent with our findings, inadequate VitD status has been suggested as a risk factor for MI and has been shown to be associated with adverse prognostic outcomes (Milazzo et al., 2017; Perez-Hernandez et al., 2016). Recently, Shareef et al. showed low VitD levels to be common in patients with MI (Shereef and Kandeel, 2019). In another recent study on young patients below forty years of age, Vit D deficiency was shown to be associated with higher risk for MI (Islam et al., 2019). Low serum VitD has been linked with increased risk of mortality in MI patients (Kestenbaum et al., 2011). Also, one study demonstrated low Vit D levels in patients with acute MI to be associated with adverse outcomes including large infarct size following thrombolysis (Separham et al., 2017).

Our findings of raised serum PTH in MI patients are concordant with results reported previously showing higher PTH to be associated with adverse cardiovascular outcomes. A recent meta-analysis linked higher serum PTH levels with an elevated risk of developing CVD events (Ballegooijen et al., 2013). A high proportion of ACS patients have been shown to have raised PTH which was associated with unfavorable clinical outcome (Ruiz et al., 2018). Raised PTH following an acute attack of MI has also been suggested to increase the risk for subsequent heart failure (Ballegooijen et al., 2013; Firouzi et al., 2020; Kestenbaum et al., 2011; Ruiz et al., 2018). High PTH levels have been suggested to predict mortality in patients following MI (Obradovic et al., 2013). Heightened CVD risk including hypertensive tendency has also been suggested in patients with primary hyperparathyroidism, possibly due to effects of raised PTH and calcium levels (Fisher and Perrier, 2020). Independent of serum calcium, raised PTH levels have also been shown to be associated with an increased incidence of CVD events in patients with chronic renal failure and hemodialysis (Lishmanov et al., 2012; Nasri, 2013). Parathyroidectomy in patients with primary hyperparathyroidism has been shown to improve cardiovascular risk factors, irrespective of serum calcium levels (Beysel et al., 2019). Hoque et al. (2020) recently reported lack of association between serum PTH and ACS but their pilot study was limited by its small sample size, lack of comparative group and heterogeneity of study sample that included MI patients as well as those with unstable angina.

Apart from the small sample size, the present study was limited by its lack of control over confounding factors for vitamin D status such as dietary intake and sun exposure. Sunlight has previously been shown to have cardiovascular benefits irrespective of VitD levels (Weller, 2016). Although sun exposure was determined in the study, the disproportionate distribution on the basis of sun exposure did not permit effective comparisons. Gender-wise analysis was also not possible due to the small sample size and uneven distribution. Moreover, being a cross-sectional study, the one-time measurement of VitD and PTH may not be truly reflective of the life time status of the two parameters.

5. CONCLUSION

Lower serum VitD levels and higher serum PTH levels are a risk factor for MI, potentially through their adverse effects on lipid homeostasis. In view of these findings, there is need to revisit the traditional metabolic risk factors of CVD such as dyslipidemia in terms of their underlying mechanisms. Furthermore, future work directed at elucidating the effect of supplementation with VitD in deficient individuals on reducing the risk of MI is required. In addition to vitamin D status, PTH has cardiovascular effects which make it a potential candidate in the clinical management of MI. Randomized controlled studies may help determine whether

adequate PTH control diminishes the risk of MI. Results from such studies may also help identify the clinical utility of determining PTH levels for the risk assessment of MI.

Authors' contribution

SIAS, MZS, UYQ and IH were involved in the concept, design, definition of intellectual content, literature search, data acquisition, statistical analysis, manuscript preparation, manuscript editing and manuscript review.

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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Informed Consent

Written and oral informed consent was obtained from each study participant individually. No identifying information of any participant was included in this manuscript.

Ethical Approval

The study was approved by the Research Committee of the College of Pharmacy, University of Hafr Al-Batin, Saudi Arabia (RCCP/2020/01/CardiacHealth).

Data and materials availability

All data associated with this study are present in the paper.

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